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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,302	01/26/2001	Martha J. Whitehouse	1543.201 (5784-81A)	7656

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/15/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/771,302	Applicant(s) WHITEHOUSE, MARTHA J.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-49* is/are rejected.

7)☒ Claim(s) *50-52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The information disclosure statement filed 16 April 2001 (Paper No. 3) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The Formal Drawings filed 30 July 2001 (Paper No. 4) have been entered.

The amendment filed 06 September 2002 (Paper No. 13) has been entered in full. Claims 1-34 were cancelled. New claims 35-52 were added. Claims 35-52 are under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35, 36, 43 and 44 rejected under 35 U.S.C. 103(a) as being unpatentable over Deisher *et al.* (U.S. Patent No. 5,989,866). The instant claims are generally drawn to treating a human patient for congestive heart failure comprising administering recombinant FGF-2 or an angiogenically active fragment or an angiogenically active mutein thereof into a coronary vessel or peripheral vein.

Deisher teaches polynucleotide and polypeptide molecules of zFGF-5, a novel member of the FGF family (abstract). Deisher teaches homology alignments with human FGF-2 (figures 1 and 2; column 5, lines 41-59; column 8, lines 20-45 and column 14, lines 37-62). The therapeutical applications include treatment of heart disease (column 2, lines 40-57 and column 3, lines 30-32). The invention provides pharmaceutical compositions comprising a purified FGF homolog polypeptide, in combination with a pharmaceutically acceptable vehicle (column 4, lines 65-67). The polypeptides may be used in treatment of disorders associated with congestive heart failure (column 25, lines 30-34) and other indications where angiogenesis is of benefit (column 25, lines 35-46). Deisher teaches intravenous administration of zFGF-5 by bolus injection or infusion. Doses are in the range of 0.1 to 100 ug/kg of patient weight per day, preferably 0.5-20ug/kg per day. Thus Deisher teaches a method for treating a human patient for congestive heart comprising administering an angiogenically active fragment or an angiogenically active mutein of FGF-2 (zFGF-5). Deisher does not teach administering to a patient a unit dose comprising from about .008 mg to 7.2 mg. However, Deisher teaches administration of a unit dose range of zFGF-5 between 50ng/day-100ug/day to rats (column 29, lines 64-67). Deisher also states that determination of dose is within the level of ordinary skill in the art (column 26, lines 36-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Deisher to treat congestive heart failure because Deisher states that FGF-2 has been shown to play a role in avian cardiac

development and induces coronary collateral development in dogs. The motivation and expected success is provided by the fact that FGF induces angiogenesis, which is valuable in the treatment of heart disease and the experiments of Deisher which demonstrate that zFGF-5 has the *in vivo* activity of inducing cardiac mitogenesis (Examples 4 and 5). Although the reference does not teach administering a unit dose range of .008 mg to 7.2 mg to patients, these adjustments are a matter of judicial selection. Routine optimization is well within the purview of the skilled artisan.

Claims 37 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deisher *et al.* (U.S. Patent No. 5,989,866) in view of Fiddes *et al.* (U.S. Patent No. 5,604,293). The teachings of Deisher are described above. Deisher does not teach administering recombinant FGF-2 comprising the sequence of SEQ ID NO:2. Fiddes teaches a recombinant FGF-2 protein comprising the sequence of SEQ ID NO:2 (Figure 4 and column 3, lines 48-49). Fiddes states that the invention provides the tools for synthesis and manipulation of fibroblast growth factors useful in effecting damaged myocardial tissue (column 3, lines 11-19). Fiddes teaches intravenous administration of FGF-2 (column 8, lines 30-41).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Deisher to treat congestive heart failure using the protein (FGF-2) disclosed by Fiddes. The motivation and expected success is provided by Deisher who teaches that FGF-2 has been shown to play a role in cardiac

development and coronary collateral development and Fiddes who teaches administration of FGF-2.

Claims 38-41,42,47-49, are rejected under 35 U.S.C. 103(a) as being unpatentable over Deisher *et al.* (U.S. Patent No. 5,989,866) in view of Wilson *et al.* (U.S. Patent No. 5,612,211) and Unger *et al.* (U.S. Patent No. 5,244,460). The teachings of Deisher are described above. Deisher does not teach the administration of heparin or the administration of recombinant FGF-2 comprising the sequence of SEQ ID NO:2 or angiogenically active fragment or muteins thereof into coronary vessels.

Wilson states that FGF has been used for the treatment of ischemic heart disease where it was found to increase blood flow in the heart for sustained periods of after myocardial infarction and that bFGF (a.k.a. FGF-2) appears to induce neovascularization (column 6, lines 1-2). Wilson teaches that heparin may be used according to the present invention to potentiate the stimulatory effect of concentrations of an FGF (column 12, line 52-63). A therapeutically effective amount of at least one FGF optionally in combination with a therapeutically effective amount of at least one CSF and /or heparin may be administered by various routes including intravenously (column 14, lines 42-50). Wilson teaches administration of FGF dosage range of .02 ug/kg-2.0 mg/kg body weight or any range therein (column 15, lines 39-54). Wilson states that the methods of the present invention contemplates the use of at least one CSF and/or heparin, such as 1,2,3,4,5,6,7,8,9 or 10 heparins and/or CSFs or any range therein in combination with at least one FGF (column 16, lines 36-43). Although, Wilson

does not teach exact heparin concentrations or administration of heparin within 30 minutes of administering recombinant FGF-2 of SEQ ID NO:2 or said angiogenically active fragment or said angiogenically active mutein thereof, one skilled in the art would have been motivated to modify Wilson *et al.* to include the adjustments of conventional working conditions such as concentrations and times points of administration.

Unger teaches the administration of drugs into the coronary artery (abstract, and column 4, lines 18-52). Unger states that there is a need to target agents directly to the heart in order to promote the growth of new cardiac blood vessels and a need for the method to treat patients suffering with atherosclerosis of the coronary arteries (column 3, lines 58-67). Unger teaches the administration of bFGF (FGF-2) in amounts between 50-700 ug into the coronary artery (column 6, lines 32-38; column 7, lines 54-67 and column 8, lines 15-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Deisher to treat congestive heart failure using the heparin teachings disclosed by Wilson and coronary artery teachings disclosed by Unger. The motivation and expected success is provided by Wilson, who teaches that heparin potentiates the stimulatory effect of FGF and Unger who teaches methods comprising administering into a coronary artery, bFGF (FGF-2) for treating a damaged heart.

Claim Objections

Claims 50-52 are objected to because the instant claims depend from rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

RMD
November 13, 2002